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Title: Association between diabetes mellitus and incidence and case-fatality after stroke due to intracerebral haemorrhage: a retrospective population-based cohort study

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Short title: Diabetes mellitus and intracerebral haemorrhage

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Abstract

We investigated the associations between types of diabetes and ICH incidence and case-fatality after ICH, in a retrospective cohort study of people aged 40-89 years in Scotland 2004-2013 using linkage of population-based records of diagnosed diabetes, hospital discharges and deaths. We calculated ICH incidence and 30-day case-fatality after hospital admission for ICH and their relative risks (RR) and 95% confidence intervals (95%CI) for people with type 1 or type 2 diabetes compared to people without diabetes adjusting for age, sex and socio-economic status (SES). There were 77, 1275 and 9778 incident ICH and case-fatality (95% CI) was 44 (33, 57)%, 38 (35, 41)% and 36% (35, 37)% in people with type 1, type 2 and without diabetes, respectively. In comparison to the non-diabetic population, type 1 diabetes was associated with a higher incidence of ICH (1.74, 95%CI 1.38-2.21) and case-fatality after ICH (1.35, 95%CI 1.01-1.70), after adjustment for age, sex and SES. Small increases in ICH incidence 1.06, 95%CI 0.99-1.12) and case-fatality 1.04, 95%CI 0.96-1.13) in people with type 2 diabetes compared to non-diabetic people were not statistically significant.

Keywords: Case fatality, Epidemiology, Haemorrhagic stroke, Incidence, Intracerebral haemorrhage, Risk factors, Type 1 diabetes, Type 2 diabetes

Introduction

Uncertainties remain about the association between diabetes mellitus and the incidence of intracerebral haemorrhage (ICH) and case fatality after ICH (1-3). Previous studies have not stratified analyses by type of diabetes and variations in individual studies may be partly explained by differential effects of type of diabetes on ICH. It is important to understand the risk of ICH among people with diabetes to inform decisions about use of anti-thrombotic treatment for primary and secondary prevention of other cardiovascular diseases.

We investigated the associations between diabetes and the incidence and 30-day case-fatality after ICH compared to the non-diabetic population separately for type 1 and type 2 diabetes.

Methods

In a nation-wide population-based retrospective cohort study in 2004-2013, we linked population-based data from the national register of diagnosed diabetes (Scottish Care Information-Diabetes Collaboration [SCI-DC]); and records of hospital discharges and deaths in Scotland. SCI-DC is populated by daily downloads from primary and secondary care and is estimated to include >99% of people with diagnosed diabetes in Scotland since 2004 (S1, S2, S3). Classification of type of diabetes was based on an algorithm that started with the initial record of type of diabetes and re-classification of the diagnosis of type 1 to type 2 diabetes if either of the following criteria were met: there were recurrent records of sulfonylurea prescription or there were no records of insulin prescription.

We calculated the age-, sex- and socio-economic status (SES)-adjusted relative risk (RRs) and 95%CIs for the incidence of ICH (both fatal ICH in the community and ICH resulting in hospital admission) and 30-day case-fatality after hospital admission for ICH in people with type 1 and type 2 diabetes compared to absence of diabetes. We compared the age-standardised ICH incidence in this cohort with previous population-based cohort studies performed in Britain. As the other studies reported ICH incidence in people of all ages, we

calculated ICH incidence in our cohort in people of all ages, combining people with and without diabetes.

Individual-level data on prevalence of hypertension and use of anti-thrombotic drugs – which are known risk factors for ICH (2, 4) were not available for the non-diabetic population in this study. However, we investigated the potential for confounding by hypertension (using anti-hypertensive treatment as a proxy) and anti-thrombotic drug use by using individual level data from SCI-DC and aggregated data on age- and sex-stratified national prescribing data for the whole population for 2009 (the mid-year of the study period). Further details of the methods are provided in file S1 of the supplementary material. We estimated proportions of people receiving each drug class by age, sex and diabetes status, and used chi-square tests to assess whether proportions of people receiving prescriptions for these drugs differed by diabetes status.

Results

Participants

After excluding people with missing SES (n=1144) and people with diabetes other than type 1 or type 2 (n=1389), we included 14,671 people with type 1 diabetes, 189,769 people with type 2 diabetes and 2,427,087 people without diabetes (Figure S1). Compared to the population without diabetes, there was a larger proportion of men than women among people with diabetes (p=0.06 for type 1 and p<0.0001 for type 2 diabetes), people with type 1 diabetes were younger (p=0.05) and people with type 2 diabetes were older (p<0.001). Duration of diabetes was longer and HbA1c was higher in people with type 1 than type 2 diabetes (Table 1). Proportions of people with systolic blood pressure (BP) recorded ≤ 140 mmHg were 79% and 74.5%, Body Mass Index (BMI)<25 were 38.1% and 13% and

total cholesterol level $\leq 5\text{mmol/l}$ were 71.5% and 74.1% for type 1 and type 2 diabetes, respectively.

ICH incidence

11,130 people were admitted to hospital for ICH or died from ICH prior to hospital admission during 2004-2013: 77 (0.7%) among people with type 1 diabetes, 1275 (11.5%) with type 2 diabetes, and 9778 (87.8%) without diabetes. After adjustment for age, sex and SES, type 1 diabetes was associated with a higher ICH incidence ($p < 0.0001$), but there was no evidence of an association with type 2 diabetes ($p = 0.091$) compared to the non-diabetic population. There was no interaction between diabetes and sex ($p = 0.89$ for type 1 and $p = 0.77$ for type 2 diabetes) and between diabetes and SES on ICH incidence for either type of diabetes ($p = 0.20$ for type 1 and $p = 0.05$ for type 2 diabetes; Table 1).

Comparison with previous British population-based cohort studies

The age-standardised ICH incidence in the total population of Scotland of all ages was 12.9 per 100,000 person-years (95%CI, 12.2-13.6). Compared to British population-based studies of ICH incidence in entire populations, the estimate in this study was similar to those identified in studies by Smeeton (S4), Samarasekera (S5), Bamford (S6) and Syme (5) but higher than the one found by Rothwell (6) (Figure S2).

ICH case-fatality

8900 (80%) of the 11,130 people with incident ICH were admitted to hospital. 30-day case-fatality after hospital admission was higher in people with type 1 diabetes than in people without diabetes after adjustment for age, sex and SES ($p = 0.0424$). Case-fatality following hospital admission for ICH was similar in people with type 2 diabetes and without diabetes

after adjustment for age, sex and SES ($p=0.3234$). There was no interaction between diabetes and sex ($p=0.26$ for type 1 and $p=0.82$ for type 2 diabetes) and between diabetes and SES on case-fatality for either type of diabetes ($p=0.31$ for type 1 and $p=0.68$ for type 2 diabetes; Table 2).

Comparison in anti-hypertensive and anti-thrombotic drugs by diabetes status

People with type 1 and type 2 diabetes were significantly ($p<0.0001$) more likely to receive treatment with anti-hypertensive and anti-thrombotic drugs than people without diabetes in all age and sex strata with the exception of people with type 1 diabetes aged 80-89 (table S1).

Discussion

In this first study investigating the association between diabetes types and ICH, we found that people with type 1 diabetes had a higher ICH incidence and 30-day case-fatality after ICH after adjustment for age, sex and SES, compared to the non-diabetic population. Small, non significant associations were observed between type 2 diabetes and ICH incidence and case-fatality in similar analyses. We undertook a sensitivity analysis for the subgroup admitted to hospital, which did not change the overall associations (age-, sex- and SES-adjusted RR of ICH 1.73, 95%CI 1.31-2.23 for type 1 and 1.07, 95%CI 0.99-1.15 for type 2 diabetes among people admitted to hospital) suggesting that the inclusion of ICH deaths outside hospital does not affect the association with diabetes.

The shorter duration of diabetes and the better control of glycaemic level and other vascular risk factors (such as hypertension) in people with type 2 than type 1 diabetes could partly explained the absence of significant association between type 2 diabetes and ICH incidence. It is also possible that people with undiagnosed type 2 diabetes were included in the non-diabetic group because there is no systematic population-screening programme for diabetes in Scotland, which could have underestimated the association between type 2 diabetes and ICH.

The strengths of the study include the use of a population-based study using data from national registers minimising selection bias and providing a large enough sample size to investigate the association between type 1 diabetes and ICH, although it is possible that the association reflects a chance finding. We were able to adjust associations for the potential confounding factors of age, sex, and SES and to investigate potential effect modification of diabetes by these factors that has been observed previously (7-9). However, we cannot exclude the possibility of residual confounding from risk factors for ICH incidence such as hypertension and anti-thrombotic drug use (2, 4). Although individual data on BP and anti-thrombotic drugs are available within the diabetes register, similar data are not available for the non-diabetic population. We are therefore unable to adjust for differences in risk factor and treatment patterns between people with and without diabetes. Our findings suggest that people with diabetes are more likely to receive treatment with anti-hypertensive and anti-thrombotic drugs. It is likely that adjustment for exposure to anti-thrombotic drugs would reduce the strength of the association between diabetes and ICH incidence. Adjustment for hypertension and anti-hypertensive drug on the association between diabetes and ICH incidence may also have similar effects although people with diabetes may receive more intensive anti-hypertensive treatment than people without diabetes. Uncertainties remain about the association between statin use, cholesterol levels, BMI, smoking and incidence of ICH (10-12).

Rothwell's study, which identified the lowest age-standardised ICH incidence among British studies, was conducted in a very wealthy area of Britain, however, our analyses of the Scottish population indicated that SES was a minor confounder in the association between diabetes and ICH.

The CALIBER study identified a higher risk of ICH as the first presentation of cardiovascular disease among people with type 2 diabetes compared with absence of diabetes based on 84

and 2265 ICH respectively after adjustment for several factors including age, sex, deprivation, hypertension, cholesterol, statin and anti-hypertensive drugs (hazard ratio=1.28, 95%CI 1.02-1.62) (13). There were slight differences in age, other characteristics and study period between our study and the CALIBER study, which had to exclude 15% of people without a code for type of diabetes. The apparent discrepancy between the association between type 2 diabetes and ICH in the CALIBER study and ours may reflect chance as the CIs for the estimates of RR overlap. Our findings add to those of the CALIBER study by describing the association between diabetes and ICH regardless of whether it occurs as the first or subsequent cardiovascular event and comparing the effects of type 1 and type 2 diabetes on both ICH incidence and case-fatality.

The only study reporting the association between the incidence of haemorrhagic stroke (i.e. subarachnoid haemorrhage and ICH combined) and types of diabetes found a similar pattern of results to ours, after adjusting for factors including age, hypertension, alcohol intake and aspirin use (RR 3.8, 95%CI 1.2-11.8 for type 1 and RR 1.0, 95%CI 0.7-1.4 for type 2 diabetes) (14). However, this study involved only women and no other studies stratified by type of diabetes have been published. The higher risk of ICH in people with diabetes may be mediated by the association between diabetes and cerebral small vessel disease (15). The higher case-fatality in type 1 diabetes may be explained by the association between hyperglycaemia and ICH volume expansion, both of which are independent predictors of death after ICH (S7, S8). Further large studies of well-characterised populations are required to identify to what extent the associations we found could be explained by confounding and to describe the role of diabetes factors such as duration of diabetes and HbA1c as risk factors for ICH incidence and case-fatality. Current approaches to managing cardiovascular risk among people with type 2 diabetes in Scotland do not appear to be associated with increased risk of ICH incidence or case-fatality.

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